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(54) **CRYSTALLINE**

**R-(R\*,R\*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-(PHENYLAMINO)CARBONYL-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)**

**KRISTALLINES**

**(R-(R\*,R\*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-((PHENYLAMINO)CARBONYL)-1H-PYRROL-1-HEPTANCARBONSÄURE HEMI CALCIUM SALZ (ATORVASTATIN)**

**FORMES CRISTALLINES D'HEMI-SEL DE CALCIUM D'ACIDE**

**R-(R\*,R\*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-(PHENYLAMINO)CARBONYL-1H-PYRROLE-1-HEPTANOIQUE (ATORVASTATINE)**

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(56) References cited:  
**EP-A- 0 409 281 WO-A-94/16693**  
**US-A- 5 316 765**

- **TETRAHEDRON LETT. (1992), 33(17), 2283-4**  
**CODEN: TELEAY; ISSN: 0040-4039, 1992,**  
**XP000608147 BAUMANN, KELVIN L. ET AL: "The**  
**convergent synthesis of CI-981, an optically**  
**active, highly potent, tissue-selective inhibitor**  
**of HMG-CoA reductase"**

### Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

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**EP 0 848 705 B1**

## Description

## BACKGROUND OF THE INVENTION

[0001] The present invention relates to a novel crystalline form of atorvastatin which is known by the chemical name [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for its production and isolation, to pharmaceutical compositions which include this compound and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compound of the present invention is useful as inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and is thus useful hypolipidemic and hypocholesterolemic agent.

[0002] United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain *trans*-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones, including *trans* ( $\pm$ )-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

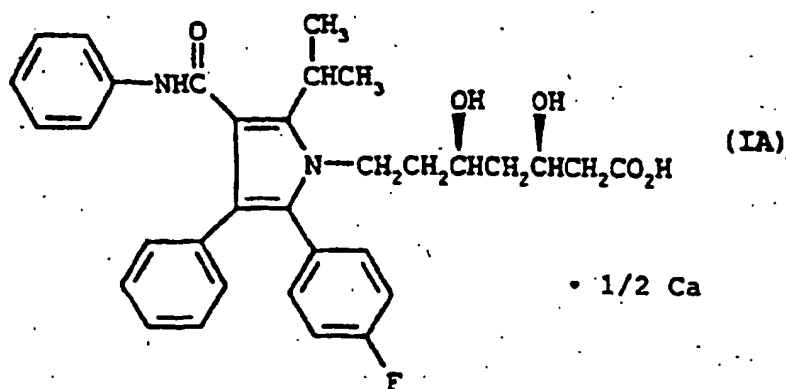
[0003] United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of *trans*-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

[0004] United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

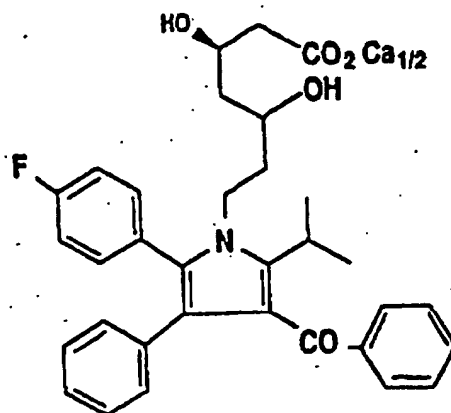
[0005] Atorvastatin is prepared as its calcium salt, i.e., [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

[0006] Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to largescale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

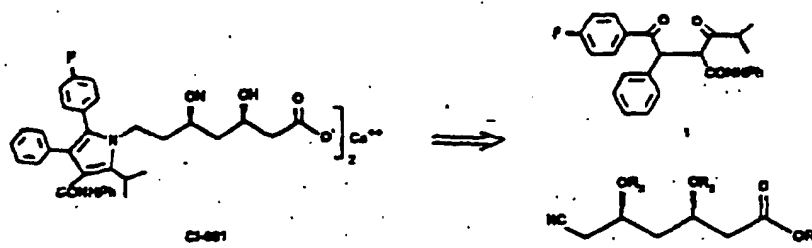
[0007] The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture. WO-A-94/16693 discloses an oral pharmaceutical composition for treating hypercholesterolemia or hyperlipidemia containing an advantageous formulation for stabilizing the HMG-CoA coenzyme A inhibitor, CI-981 Hemi-Calcium, of formula (IA) with effective amounts of calcium carbonate.



[0008] US-A-5 316 765 discloses a method for ameliorating reductions of coenzyme Q<sub>10</sub> in cardiomyopathy patients receiving an HMG-CoA reductase inhibitor comprising administering concurrently with said HMG-CoA reductase inhibitor coenzyme Q<sub>10</sub> at a concentration sufficient to raise serum levels of coenzyme Q<sub>10</sub> to at least 2.0  $\mu$ g/ml, wherein as said HMG-CoA reductase inhibitor there may be used CI-981 having the following formula:



[0009] Tetrahedron Letters, Vol. 33, No. 17, pp. 2283-2284, 1992, Baumann, Kelvin et al. describe the synthesis of CI-981 and the key chiral intermediate (2):



[0010] EP-A-0 409 281 discloses [R-(R\*,R\*)]-2-(4-fluorophenyl)- $\beta,\delta$ -dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; a process for their preparation and pharmaceutically acceptable salts thereof.

[0011] We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the present invention provides atorvastatin in a new crystalline form designated Form I.

[0012] Form I atorvastatin hydrate consists of a smaller particles and a more uniform size distribution than the previous amorphous product and exhibits more favorable filtration and drying characteristics. Additionally, Form I atorvastatin hydrate is purer and more stable than the amorphous product.

#### SUMMARY OF THE INVENTION

[0013] Accordingly, the present invention is directed to

1. Crystalline Form I atorvastatin (i.e. [R-(R\*, R\*)]-2-(4-fluorophenyl)- $\beta,\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate, having an X-ray powder diffraction pattern containing the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 19.485 and 21.626;

2 Crystalline Form I atorvastatin hydrate according to item 1, wherein the X-ray powder diffraction pattern further contains the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 17.075 and 23.734 ;

3. Crystalline Form I atorvastatin hydrate according to item 2, wherein the X-ray powder diffraction pattern further contains the following  $2\theta$  values measured using  $\text{CuK}\alpha$  radiation: 9.150, 9.470, 10.266, 11.853, 21.960, 22.748 and 23.335 ;

4. Crystalline Form I atorvastatin hydrate, having an X-ray powder diffraction pattern containing the following  $2\theta$

values measured using  $\text{CuK}_\alpha$  radiation: 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734', 24.438, 28.915 and 29.234 ;

5 5. Crystalline Form I atorvastatin hydrate, having an X-ray powder diffraction pattern containing at least one of the following 2 $\theta$  values measured using  $\text{CuK}_\alpha$  radiation: 11.853 or 21.960;

6. Crystalline Form I atorvastatin hydrate, characterized by solid-state  $^{13}\text{C}$  nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8;

10 7. The crystalline Form I atorvastatin hydrate according to any one of the preceding items containing 1 to 8 moles of water;

15 8. The crystalline Form I atorvastatin hydrate according to any one of the preceding items containing 3 moles of water;

9. A pharmaceutical composition, comprising crystalline Form I atorvastatin hydrate according to any one of the preceding items in admixture with at least one pharmaceutically acceptable excipient, diluent or carrier ;

20 10. A pharmaceutical composition according to item 9 , in the form of tablets, pills, dispersible granules, cachets, capsules, powders, lozenges, suppositories or retention enemas, and

11. Use of a crystalline Form I atorvastatin hydrate according to any one of items 1 to 8 in the medicine.

25 **[0014]** As inhibitors of HMG-CoA, the novel crystalline form of atorvastatin is a useful hypolipidemic and hypocholesterolemic agent.

#### BRIEF DESCRIPTION OF THE DRAWINGS

30 **[0015]** The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1 and 2 short particulars of which are given below.

##### Figure 1

35 **[0016]** Diffractogram of Form I atorvastatin hydrate ground for 2 minutes (Y-axis = 0 to maximum intensity of 3767.50 counts per second (cps))

##### Figure 2

40 **[0017]** Solid-state  $^{13}\text{C}$  nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin hydrate.

#### DETAILED DESCRIPTION OF THE INVENTION

45 **[0018]** Crystalline Form I atorvastatin hydrate may be characterized by its X-ray powder diffraction pattern and/or by their solid state nuclear magnetic resonance spectrum (NMR).

#### X-RAY POWDER DIFFRACTION

##### Form I Atorvastatin

50 **[0019]** Form I atorvastatin hydrate was characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of Form I atorvastatin hydrate was measured on a Siemens D-500 diffractometer with  $\text{CuK}_\alpha$  radiation.

##### Equipement

55 **[0020]** Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SO-

CABIM 1986, 1992).

[0021]  $\text{CuK}_\alpha$  radiation (20 mA, 40 kV,  $\lambda = 1.5406 \text{ \AA}$ ) Slits I and II at  $1^\circ$ ) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at  $1^\circ$  and IV at  $0.15^\circ$ ).

## 5 Methodology

[0022] The silicon standard is run each day to check the X-ray tube alignment.

[0023] Continuous  $\theta/2\theta$  coupled scan:  $4.00^\circ$  to  $40.00^\circ$  in  $2\theta$ , scan rate of  $6^\circ/\text{min}$ : 0.4 sec/ $0.04^\circ$  step.

10 [0024] Sample tapped out of vial and pressed onto zerobackground quartz in aluminum holder. Sample width 13-15 mm.

[0025] Samples are stored and run at room temperature.

## Grinding/Sieving

15 [0026] Grinding is used to minimize intensity variations for the diffractogram disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used. Grinding was done in a small agate mortar and pestle. The mortar was held during the grinding and light pressure was applied to the pestle.

20 [0027] Table 1 lists the  $2\theta$ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of  $>20\%$  for crystalline Form I atorvastatin hydrate. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

TABLE 1.

Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Than 20% for Form I Atorvastatin hydrate				
$2\theta$	d	Relative Intensity ( $>20\%$ ) No Grinding	Relative Intensity ( $>20\%$ )*Ground 2 Minutes	
9.150	9.6565	37.42	42.60	
9.470	9.3311	46.81	41.94	
10.266	8.6098	75.61	55.67	
10.560	8.3705	24.03	29.33	
11.853	7.4601	55.16	41.74	
12.195	7.2518	20.03	24.62	
17.075	5.1887	25.95	60.12	
19.485	4.5520	89.93	73.59	
21.626	4.1059	100.00	100.00	
21.960	4.0442	58.64	49.44	
22.748	3.9059	36.95	45.85	
23.335	3.8088	31.76	44.72	
23.734	3.7457	87.55	63.04	
24.438	3.6394	23.14	21.10	
28.915	3.0853	21.59	23.42	
29.234	3.0524	20.45	23.36	

\* The second relative intensity column gives the relative intensities of the diffraction lines on the original diffractogram after 2 minutes of grinding.

## 50 SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

### Methodology

55 [0028] All solid-state  $^{13}\text{C}$  NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., *J. Mag. Res.*, 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced

to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988; 76:54).

[0029] Table 2 shows the solid-state NMR spectrum for crystalline Form I atorvastatin hydrate.

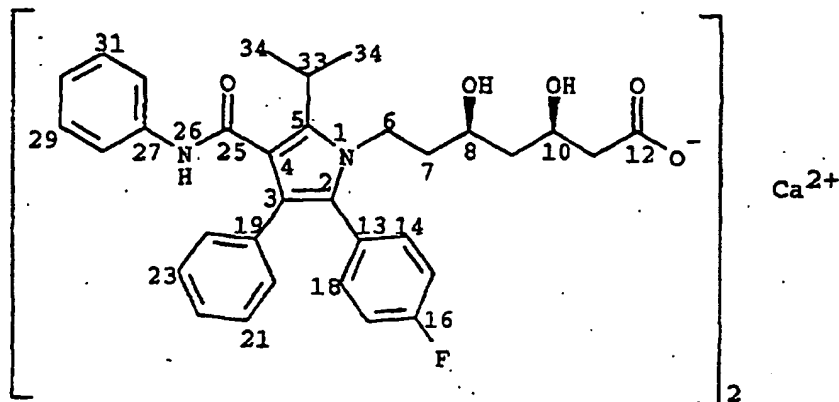


TABLE 2

Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin hydrate	
Assignment (7 kHz)	Chemical Shift
C12 or C25	182.8
C12 or C25	178.4
C16	166.7 (broad) and 159.3
Aromatic Carbons C2-C5, C13-C18, C19-C24, C27-C32	137.0 134.9 131.1 129.5 127.6 123.5 120.9 118.2 113.8
C8,C10	73.1 70.5 68.1 64.9
Methylene Carbons C6, C7, C9, C11	47.4 41.9 40.2
C33	26.4 25.2

TABLE 2 (continued)

Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin hydrate	
Assignment (7 kHz)	Chemical Shift
C34	21.3

[0030] Crystalline Form I atorvastatin hydrate of the present invention exists in hydrated forms. Crystalline Form I atorvastatin hydrate contains about 1 to 8 mol of water. Preferably, Form I atorvastatin hydrate contains 3 mol of water.

[0031] The present invention provides a process for the preparation of crystalline Form I atorvastatin hydrate which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Form I atorvastatin hydrate.

[0032] The precise conditions under which crystalline Form I atorvastatin hydrate is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

[0033] Thus, for example, crystalline Form I atorvastatin hydrate may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

[0034] When the starting material for the preparation of the desired crystalline Form I atorvastatin hydrate is a solution of the corresponding sodium salt, one preferred preparation involves treating a solution of the sodium salt in water containing not less than about 5% v/v methanol, preferably about 5% to 33% v/v methanol, particularly preferred about 10% to 15% v/v methanol, with an aqueous solution of calcium acetate, preferably at an elevated temperature at up to about 70°C such as, for example, about 45-60°C, particularly preferred about 47-52°C. It is preferable to use calcium acetate and, in general, 1 mole of calcium acetate to 2 moles of the sodium salt of atorvastatin. Under these conditions, calcium salt formation as well as crystallization should preferably be carried out at an elevated temperature, for example within the abovementioned temperature ranges. It has been found that it may be advantageous to include in the starting solution a small amount of methyl tert-butyl ether (MTBE) such as, for example, about 7% w/w. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin hydrate to the crystallization solution in order to consistently produce crystalline Form I atorvastatin hydrate.

[0035] When the starting material is amorphous atorvastatin or a combination of amorphous and crystalline Form I Atorvastatin hydrate the desired crystalline Form I Atorvastatin hydrate may be obtained by suspending the solid in water containing up to about 40% v/v, such as, for example, about 0% to 20% v/v, particularly preferred about 5% to 15% v/v co-solvent such as, for example, methanol, ethanol, 2-propanol, acetone, and the like until conversion to the required form is complete, followed by filtration. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin hydrate to the suspension in order to ensure complete conversion to crystalline Form I atorvastatin hydrate. Alternatively a water-wet cake consisting principally of amorphous atorvastatin can be heated at elevated temperatures such as, for example, up to about 75°C, particularly preferred about 65-70°C, until a significant amount of crystalline Form I atorvastatin hydrate is present, whereupon the amorphous/ crystalline Form I mixture can be slurried as described above.

[0036] Crystalline Form I atorvastatin hydrate is significantly easier to isolate than amorphous atorvastatin and can be filtered from the crystallization medium after cooling, and washed and dried. For example, filtration of a 50 mL slurry of crystalline Form I atorvastatin hydrate was complete within 10 seconds. A similarly sized sample of amorphous atorvastatin took more than an hour to filter.

[0037] The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

[0038] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0039] In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

[0040] In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0041] The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0042] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0043] Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0044] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

[0045] Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0046] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0047] The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0048] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0049] In therapeutic use as hypolipidemic and/or hypocholesterolemic agents, the crystalline Form I atorvastatin hydrate utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

[0050] The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

#### EXAMPLE 1

[R-(R\*,R\*)]-2-(4-Fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin hydrate)

#### Method A

[0051] A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin hydrate (1.1 kg in 11 L water and 5 L methanol) shortly



after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I atorvastatin hydrate (72.2 kg).

#### Method B

[0052] Amorphous atorvastatin (9 g) and crystalline Form I atorvastatin hydrate (1g) are stirred at about 40°C in a mixture of water (170 mL) and methanol (30 mL) for a total of 17 hours. The mixture is filtered, rinsed with water, and dried at 70°C under reduced pressure to give crystalline Form I atorvastatin hydrate (9.7 g).

#### Claims

1. Crystalline Form I atorvastatin (i.e. [R-(R\*, R\*)]-2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt) hydrate, having an X-ray powder diffraction pattern containing the following 2 $\theta$  values measured using CuK $\alpha$  radiation: 19.485 and 21.626.
2. Crystalline Form I atorvastatin hydrate according to claim 1, wherein the X-ray powder diffraction pattern further contains the following 2 $\theta$  values measured using CuK $\alpha$  radiation: 17.075 and 23.734.
3. Crystalline Form I atorvastatin hydrate according to claim 2, wherein the X-ray powder diffraction pattern further contains the following 2 $\theta$  values measured using CuK $\alpha$  radiation: 9.150, 9.470, 10.266, 11.853, 21.960, 22.748 and 23.335.
4. Crystalline Form I atorvastatin hydrate, having an X-ray powder diffraction pattern containing the following 2 $\theta$  values measured using CuK $\alpha$  radiation: 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 and 29.234.
5. Crystalline Form I atorvastatin hydrate, having an X-ray powder diffraction pattern containing at least one of the following 2 $\theta$  values measured using CuK $\alpha$  radiation: 11.853 or 21.960.
6. Crystalline Form I atorvastatin hydrate, **characterized by** solid-state  $^{13}\text{C}$  nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.
7. The crystalline Form I atorvastatin hydrate according to any one of the preceding claims containing 1 to 8 moles of water.
8. The crystalline Form I atorvastatin hydrate according to any one of the preceding claims containing 3 moles of water.
9. A pharmaceutical composition, comprising crystalline Form I atorvastatin hydrate according to any one of the preceding claims in admixture with at least one pharmaceutically acceptable excipient, diluent or carrier.
10. A pharmaceutical composition according to claim 9, in the form of tablets, pills, dispersible granules, cachets, capsules, powders, lozenges, suppositories or retention enemas.
11. Use of a crystalline Form I atorvastatin hydrate according to any one of claims 1 to 8 in the medicine.

#### Patentansprüche

1. Kristallines Atorvastatin(d.h. [R-(R\*,R\*)]-2-(4-Fluorphenyl)- $\beta$ , $\delta$ -dihydroxy-5- (1-methylethyl)-3-phenyl-4-[(phenyl-amino)carbonyl]-1H-pyrrol-1-heptansäure-hemicalciumsalz)-Hydrat der Form I mit einem Pulverröntgenbeugungsmuster, das die im folgenden angegebenen, unter Verwendung von CuK $\alpha$ -Strahlung ermittelten 2 $\theta$ -Werte enthält: 19,485 und 21,626.
2. Kristallines Atorvastatinhydrat der Form I gemäß Anspruch 1, wobei das Pulverröntgenbeugungsmuster ferner die

im folgenden angegebenen, unter-Verwendung von  $\text{CuK}_\alpha$ -Strahlung ermittelten  $2\theta$ -Werte enthält: 17,075 und 23,734.

3. Kristallines Atorvastatinhydrat der Form I gemäß Anspruch 2, wobei das Pulverröntgenbeugungsmuster ferner die im folgenden angegebenen, unter Verwendung von  $\text{CuK}_\alpha$ -Strahlung ermittelten  $2\theta$ -Werte enthält: 9,150, 9,470, 10,266, 11,853, 21,960, 22,748 und 23,335.
4. Kristallines Atorvastatinhydrat der Form I mit einem Pulverröntgenbeugungsmuster, das die im folgenden angegebenen, unter Verwendung von  $\text{CuK}_\alpha$ -Strahlung ermittelten  $2\theta$ -Werte enthält: 9,150, 9,470, 10,266, 10,560, 11,853, 12,195, 17,075, 19,485, 21,626, 21,960, 22,748, 23,335, 23,734, 24,438, 28,915 und 29,234.
5. Kristallines Atorvastatinhydrat der Form I mit einem Pulverröntgenbeugungsmuster, das mindestens einen der im folgenden angegebenen, unter Verwendung von  $\text{CuK}_\alpha$ -Strahlung ermittelten  $2\theta$ -Werte enthält: 11,853 und 21,960.
6. Kristallines Atorvastatinhydrat der Form I, charakterisiert durch Festkörper- $^{13}\text{C}$ -Kernresonanz mit den im folgenden angegebenen chemischen Verschiebungen in ppm (parts per million): 21,3, 25,2, 26,4, 40,2, 41,9, 47,4, 64,9, 68,1, 70,5, 73,1, 113,8, 118,2, 120,9, 123,5, 127,6, 129,5, 131,1, 134,9, 137,0, 159,3, 166,7 (breit), 178,4 und 182,8.
7. Kristallines Atorvastatinhydrat der Form I gemäß einem der vorhergehenden Ansprüche, das 1-8 Mole Wasser enthält.
8. Kristallines Atorvastatinhydrat der Form I gemäß einem der vorhergehenden Ansprüche, das 3 Mole Wasser enthält.
9. Pharmazeutische Zusammensetzung, die kristallines Atorvastatinhydrat der Form I gemäß einem der vorhergehenden Ansprüche im Gemisch mit mindestens einem pharmazeutisch akzeptablen Streckmittel, Verdünnungsmittel oder Träger enthält.
10. Pharmazeutische Zusammensetzung gemäß Anspruch 9 in Form von Tabletten, Pillen, dispergierbaren Körnchen, Kachets, Kapseln, Pulvern, Pastillen, Suppositorien oder Retentionsklistieren.
11. Verwendung eines kristallinen Atorvastatinhydrats der Form I gemäß einem der Ansprüche 1-8 in der Medizin.

## Revendications

1. Hydrate d'atorvastatine (c'est-à-dire hémi- $[\text{R}-(\text{R}^*, \text{R}^*)]-2-(4\text{-fluorophényl})-\beta, \delta\text{-dihydroxy-5-(1-méthyléthyl)-3-phényl-4-}[(\text{phénylamino})\text{-carbonyl}]-1\text{H-pyrrole-1-heptanoate de calcium}$ ), sous la forme cristalline I ayant un diagramme de diffraction des rayons X de poudre contenant les valeurs  $2\theta$  suivantes, mesurées avec la raie  $\text{K}_\alpha$  de Cu : 19,485 et 21,626.
2. Hydrate d'atorvastatine sous la forme cristalline I selon la revendication 1, où le diagramme de diffraction des rayons X de poudre contient en outre les valeurs  $2\theta$  suivantes, mesurées avec la raie  $\text{K}_\alpha$  de Cu : 17,075 et 23,734.
3. Hydrate d'atorvastatine sous la forme cristalline I selon la revendication 2, où le diagramme de diffraction des rayons X de poudre contient en outre les valeurs  $2\theta$  suivantes, mesurées avec la raie  $\text{K}_\alpha$  de Cu : 9,150, 9,470, 10,266, 11,853, 21,960, 22,748 et 23,335.
4. Hydrate d'atorvastatine sous la forme cristalline I ayant un diagramme de diffraction des rayons X de poudre contenant les valeurs  $2\theta$  suivantes, mesurées avec la raie  $\text{K}_\alpha$  de Cu : 9,150, 9,470, 10,266, 10,560, 11,853, 12,195, 17,075, 19,485, 21,626, 21,960, 22,748, 23,335, 23,734, 24,438, 28, 915 et 29,234.
5. Hydrate d'atorvastatine sous la forme cristalline I ayant un diagramme de diffraction des rayons X de poudre contenant au moins l'une des valeurs  $2\theta$  suivantes, mesurées avec la raie  $\text{K}_\alpha$  de Cu : 11,853 et 21,960.
6. Hydrate d'atorvastatine sous la forme cristalline I, **caractérisé par** une résonance magnétique nucléaire de  $^{13}\text{C}$  à l'état solide ayant les déplacements chimiques suivants, exprimés en parties par million : 21,3, 25,2, 26,4, 40,2, 41,9, 47,4, 64,9, 68,1, 70,5, 73,1, 113,8, 118,2, 120,9, 123,5, 127,6, 129,5, 131,1, 134,9, 137,0, 159,3, 166,7

(large), 178,4 et 182,8.

7. Hydrate d'atorvastatine sous la forme cristalline I selon l'une quelconque des revendications précédentes, contenant 1 à 8 moles d'eau.

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8. Hydrate d'atorvastatine sous la forme cristalline I selon l'une quelconque des revendications précédentes, contenant 3 moles d'eau.

9. Composition pharmaceutique comprenant de l'hydrate d'atorvastatine sous la forme cristalline I selon l'une quelconque des revendications précédentes en mélange avec au moins un excipient, diluant ou support pharmaceutiquement acceptable.

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10. Composition pharmaceutique selon la revendication 9, sous forme de comprimés, de pilules, de granulés dispersibles, de cachets, de capsules, de poudres, de pastilles, de suppositoires ou de lavements à garder.

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11. Utilisation d'un hydrate d'atorvastatine sous la forme cristalline I selon l'une quelconque des revendication 1 à 8 en médecine.

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FIG-1

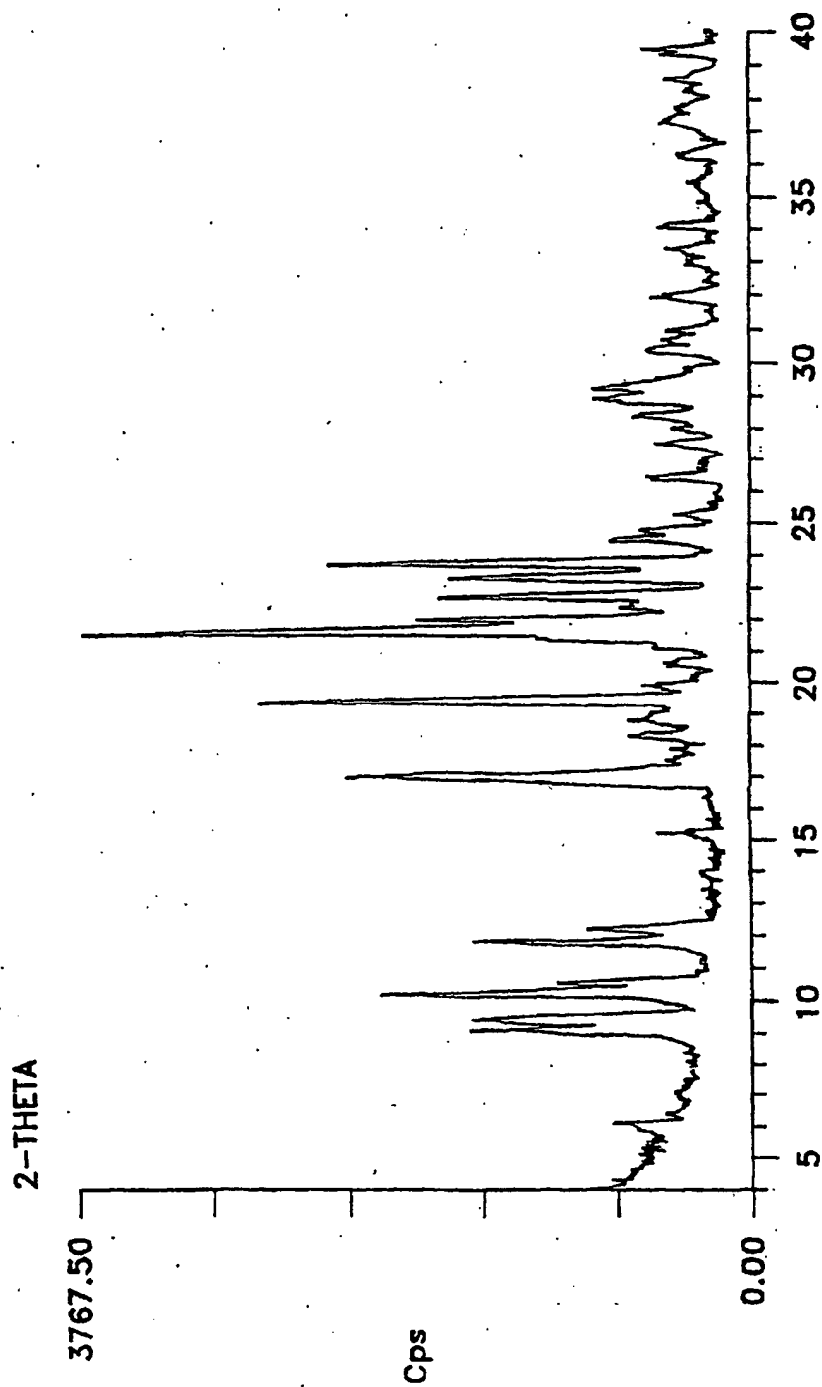


FIG-2

